APPLICATION

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TITLE: NOVEL FORMULATION

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NOVEL FORMULATION

Field of the Invention

The present invention relates to a new unit dose of budesonide, a formulation thereof, and its use for the treatment of conditions of the nose.

Background of the Invention

Glucocorticosteroids are widely used for the treatment of seasonal allergic as well as perennial rhinitis. Intranasal glucocorticosteroids reduce inflammation of the nasal mucosa including edema. In addition, they are known to suppress the recruitment of polymorphonuclear and mononuclear cells, cytokine production, and, during maintenance treatment, both early and late-phase nasal reactions.

One of the glucocorticosteroids known for intranasal use is budesonide, 16α,17α-butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20-dione.

Initially solid budesonide was used in pressurized metered dose inhaler (pMDI) preparations for intranasal administration, suitably dispensed from a specially adapted nasal inhaler. A recommended maximum daily metered dose of budesonide has been 400 μg. Later on a nasal spray preparation for delivery from a spray device was prepared, containing budesonide in the form of an aqueous suspension. The same maximum daily metered dose as for the pMDI preparation was recommended. A third formulation is a dry powder formulation.

Both the nasal pMDI inhaler device and the aqueous nasal spray device are constructed to dispense a defined unit dose at each actuation. For example, a metered unit dose of 50 μg has a recommended administration regime of one dose per nostril, four times daily, yielding a total of eight 50 μg metered doses per day. Alternatively, a metered unit dose of 100 μg

would provide the same total metered daily dose (400 μg) if administered to each nostril twice daily, for a total of four 100 μg metered doses per day.

We have now surprisingly found that a lower metered unit dose of budesonide than that previously used can be administered safely and effectively to the nose.

Disclosure of the invention

According to the invention we provide a metered unit dose of a therapeutic composition comprising budesonide in therapeutically effective amount that is less than about 40μg, said composition being suitable for nasal administration to a mammal in a single dose.

Preferably, the metered unit dose comprises from about 16 to about 40 μg of budesonide. In a preferred embodiment of the invention, the metered unit dose comprises about 32 μg of budesonide.

With this new lower metered unit dose, it is possible for the patient to take a lower metered daily dose, while still maintaining efficacy. The new lower unit dose is also convenient for the patient. Surprisingly, metered daily doses of 256 μg and 400 μg, delivered by nasal spray, were found to be equally efficacious. A metered daily dose of 256 μg can be obtained with a metered unit dose of 32 μg budesonide, dispensed 8 times daily (two doses in each nostril, twice a day).

A suitable pharmaceutical formulation of budesonide is a suspension of micronised budesonide in an aqueous vehicle.

Thus, the invention also comprises a unit dose, and preferably a metered unit dose, of a therapeutic composition comprising a therapeutically effective amount of budesonide that is less than about 40 μg, wherein the budesonide is in the form of finely divided particles and is suspended in an aqueous medium, said composition being suitable for administration to a mammal in a single dose..

Preferably, the unit dose formulation comprises from about 16 to about 40 μg of budesonide. In a most preferred embodiment of the formulation, the amount of budesonide is about 32 μg.

In a further aspect the invention comprises a suspension, preferably an aqueous suspension, comprising from about 0.6 to about 0.7 mg/ml (i.e. from about 0.06 to about 0.07% w/w) of budesonide.

In yet a further aspect the invention comprises a method of treating conditions of the nose of mammals by administering thereto a metered unit dose of 40 μg or less of budesonide.

Conditions that can be treated according to the invention include

- seasonal allergic rhinitis, i.e. pollinosis caused by pollens from ragweed, birch, grass, ceder or other plants
- perennial allergic rhinitis caused by e.g. dust mites (Dermatophagoides pteronyssinus and D. farinae), cockroaches and mammals such as cats, dogs and horses
- perennial non-allergic rhinitis
- nasal polyps, as well as prevention of post surgical nasal polyps
- chronic sinusitis
- recurrent sinusitis.

In order to form a stable suspension with a minimal tendency to agglomerate or form a sediment, a thickening agent may be included in the formulation. Examples of suitable thickening agents are microcrystalline cellulose, sodium carboxymethylcellulose, xanthan gum, carbomer, guar gum and hydroxypropyl cellulose. The thickening agent may be present at about 0.1 to 3.0% w/w of the formulation. Preferably microcrystalline cellulose and sodium carboxymethyl cellulose are present at about 0.5 to 2.5%, xanthan gum at about 0.3 to 3%, carbomer at about 0.1 to 2%, guar gum at about 0.3 to 2% and hydroxypropyl methyl cellulose at about 0.5 to 3.0%, w/w of the formulation.

Agents which make the suspension isotonic may be added. Examples are dextrose, glycerin, mannitol, sodium chloride and potassium chloride.

To obtain an efficient dispersion of the budesonide particles in the suspension, a surfactant may be used. Examples of suitable surfactants are Polysorbate 80 (Tween 80) as well as other polyoxyethylene sorbitan fatty acid esters, poloxamers, polyoxyethylene alkyl ethers and polyoxyethylene castor oil derivatives. The surfactant may be present at about 0.005 to 2% w/w of the formulation. We prefer the polyoxyethylene sorbitan fatty acid esters to be present at about 0.005 to 0.5%, poloxamers at about 0.01 to 2%, and polyoxyethylene alkyl ethers or the polyoxyethylene castor oil derivatives at about 0.01 to 1.0%, w/w of the formulation.

We also prefer the formulation to contain a suitable chelating agent, e.g. disodium edetate (EDTA). The chelating agent may be present at about 0.005 to 0.1% w/w of the formulation.

A preservative agent may be added to protect the formulation from microbial contamination. Examples of suitable preservatives are benzalkonium chloride, methylparaben, propylparaben, potassium sorbate and sodium benzoate. The preservative may be present at about 0.002 to 0.5% w/w of the formulation. Preferably benzalkonium chloride is present at about 0.002 to 0.02%, methylparaben at about 0.05 to 0.25%, propylparaben at about 0.01 to 0.2%, potassium sorbate at about 0.5 to 0.2%, and sodium benzoate at about 0.1 to 0.5%, w/w of the formulation.

The pH of the suspension may be adjusted as required. Examples of suitable pH regulating agents are strong mineral acids, e.g. hydrochloric acid. Alternatively, the pH of the system can be adjusted by balancing the acid and salt forms of preservative and chelating agent. We prefer the formulation to have a pH in the range 3.5 to 5.0 and more preferably from about 4.2 to 4.6.

The suspension medium is made essentially of purified water (as describe in the European Pharmacopoeia and the United States Pharmacopoeia), e.g. water for injection.

In the suspension the active constituent budesonide is present as small particles, where at least 90% of the small particles have a mass equivalent sphere diameter of less than 20μm, preferably at least 80% less than 10μm and most preferably at least 80% less than 7μm.

The new unit dose can suitably be dispensed from the above mentioned specially adapted nasal inhaler or spray device. Other means for administration include a simple drop pipette or a rhinyl. Pre-compression metered-dose spray pumps with dose volumes from 25 μl to 150 μl can be used, whereby the concentration of budesonide in the suspension is adjusted to give the desired unit dose of budesonide. Monospray or a bispray pump can be used; for the latter, the recommended unit dose is sequentially delivered into each nostril, for a total metered dose per administration of less than 80 μg budesonide.

According to a further feature of the invention we also provide a therapeutic method of treating or preventing conditions of the upper respiratory tract, the method comprising metering into a nostril of a mammal a unit dose of budesonide, wherein said metered unit dose comprises budesonide in a therapeutically effective amount that is less than about 40 μg.

The metered amount of budesonide is preferably less than about 320 μg per day, delivered as 8 or more unit doses each dose comprising budesonide in an amount that is less than about 40 μg.

According to a yet further feature of the invention we provide a container containing budesonide and adapted to deliver a unit dose or a formulation according to the invention.

The invention will now be described more in detail in the following non-limiting examples.

EXAMPLE 1

A unit dose comprising a suspension of 32 µg budesonide in water was prepared by mixing the following ingredients:

Ingredient	(mg)
Budesonide, micronised	0.032
Microcrystalline cellulose and carboxymethylcellulose Sodium (Avicel)	0.625
Dextrose, anhydrous	2.375
Polysorbate 80	0.008
Edetate disodium	0.005
Potassium sorbate	0.060
Hydrochloric acid	to pH 4.5
Purified water	to 50 µl (approx. 47.9 mg added)

EXAMPLE 2

A 200 litre bulk suspension, which corresponds to approximately 23,000 containers with 120 doses (32 µg/dose) of budesonide each, was prepared by mixing the following ingredients:

Ingredient	Amount (kg)
Budesonide, micronised	0.128
Microcrystalline cellulose and carboxymethylcellulose Sodium (Avicel)	2.500
Dextrose, anhydrous	9.500
Polysorbate 80	0.032
Edetate disodium	0.020
Potassium sorbate	0.240
Hydrochloric acid	to pH 4.5
Purified water	to 204.2